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Chiral amides via copper-catalysed enantioselective conjugate addition

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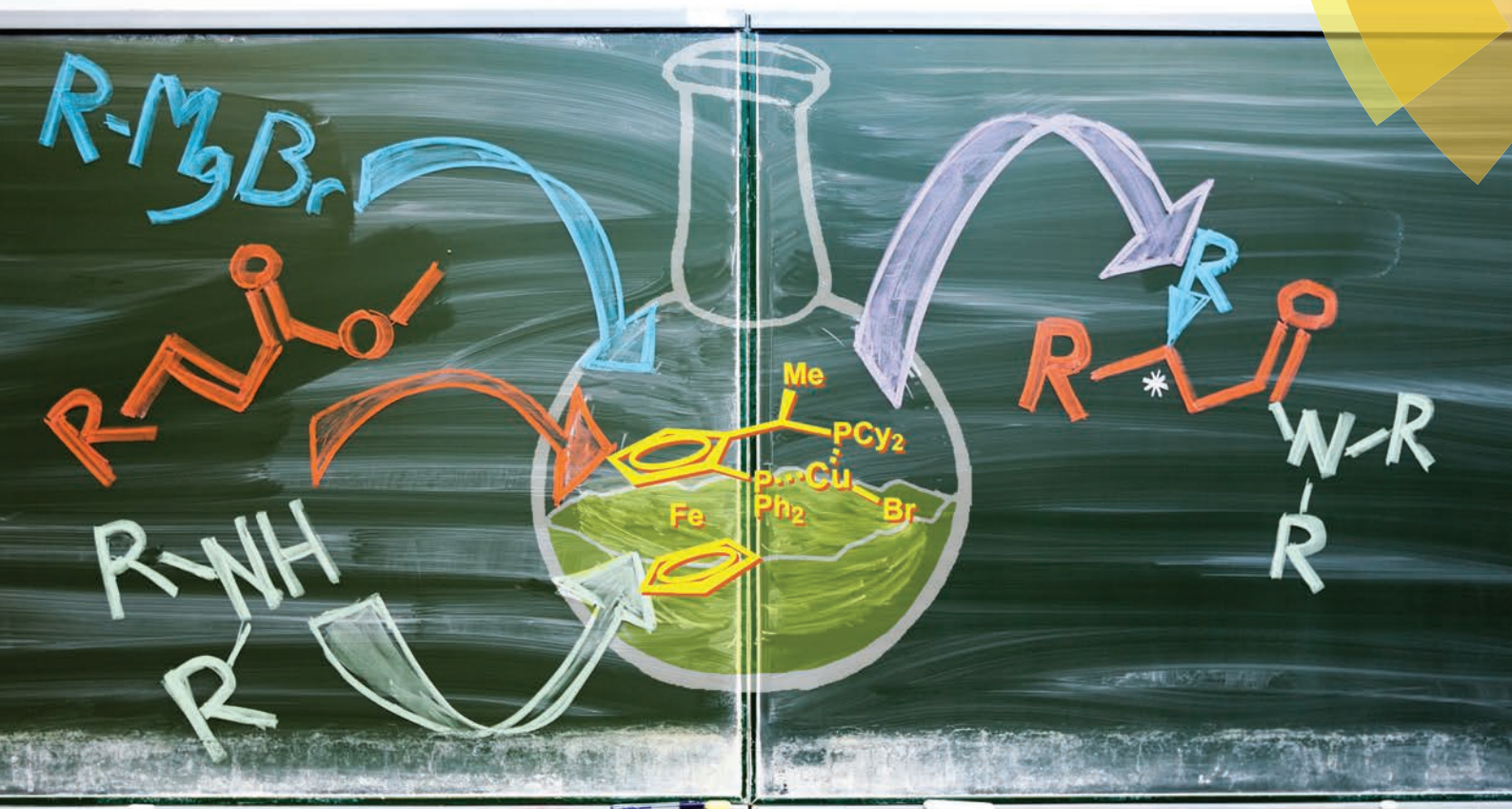
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Ben L. Feringa *et al.*

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A highly enantioselective one pot procedure for the synthesis of β -substituted amides was developed starting from the corresponding α,β -unsaturated esters. This new methodology is based on the copper-catalysed enantioselective conjugate addition of Grignard reagents to α,β -unsaturated esters and subsequent direct formation of amides by quenching the corresponding enolates with different amines. Various primary and secondary amines bearing alkyl or aryl substituents can be used giving rise to a large variety of β -substituted amides with excellent enantioselectivities.

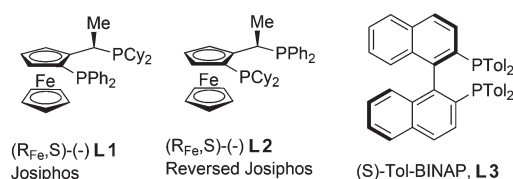


Fig. 1 Diphenylphosphine ligands used in Cu-catalysed asymmetric CA.

Introduction

The catalytic asymmetric conjugate addition (CA) of organometallic reagents to α,β -unsaturated compounds is one of the most versatile methodologies for the formation of C–C bonds.¹ In 2004, a highly enantioselective catalytic CA of Grignard reagents was reported from our laboratories.² This paved the way for the efficient enantioselective CA of Grignard reagents to α,β -unsaturated ketones,³ esters^{4,5} and thioesters⁶ using catalysts based on Josiphos type ligands (**L1** or **L2**)⁴ and various copper salts (Fig. 1). The group of Loh reported an alternative for the enantioselective CA to α,β -unsaturated esters with a catalyst consisting of Tol-BINAP (**L3**)⁵ and copper iodide (Fig. 1). Despite this progress, as far as we know only one method has been described for the enantioselective CA of Grignard reagents to α,β -unsaturated amides, with enantioselectivities ranging from 30 to 74%.⁷ This paucity in examples is probably due to the low intrinsic reactivity of α,β -unsaturated amides compared to esters and ketones.⁸ This limited the formation of chiral amides, one of the most common

structural motifs in modern pharmaceuticals and biologically active compounds.⁹

Chiral β -substituted amides can be obtained with high stereoselectivities *via* the CA of Grignard reagents to α,β -unsaturated amides bearing (*S,S*)-pseudoephedrine as a chiral auxiliary.^{7,10,11} The addition proceeds both with⁷ and without^{10,11} copper as a catalyst. However, to obtain the desired chiral β -alkyl substituted amides *via* this route two additional steps are required: one to remove the auxiliary by hydrolysis and another to obtain the corresponding amide.

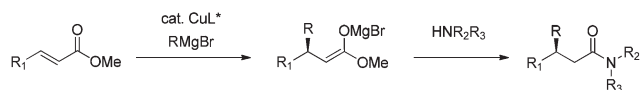
An alternative method to obtain β -alkyl substituted amides comprises the asymmetric CA of boron compounds to α,β -unsaturated amides (including 5,6-dihydro-2(1*H*)-pyridinones). This has been achieved *via* rhodium-catalysed addition of aryl-boron¹² reagents and *via* copper-catalysed addition of diboron¹³ reagents. However, these methods do not allow the introduction of alkyl groups to furnish β -alkyl substituted amides. Therefore the formation of β -alkyl substituted chiral amides remains a challenging target as this structure is present in many biologically active compounds including cyclotheonamide E4¹⁴ and orbiculamide A.¹⁵

In this context, the copper-catalysed enantioselective CA of dialkylzinc reagents to α,β -unsaturated *N*-acyloxazolidinones¹⁶ has been reported to provide the corresponding chiral β -alkyl compounds. The desired chiral β -alkyl substituted amide can be obtained from the corresponding oxazolidinones in one additional step. Furthermore, the copper-catalysed enantioselective CA to α,β -unsaturated lactams has been described with alkylzinc reagents¹⁷ and alkyl- and alkenylalanes^{17,18} giving rise to β -substituted lactams in good yields and

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Scheme 1 Catalytic asymmetric CA to esters and *in situ* formation of amides.

selectivities. There is also one example of the asymmetric CA of Me_3Al to an *N*-acylpyrrole derivative in which the corresponding methylated product is obtained in 54% yield and 96% ee.¹⁹

Recently, we discovered that β -alkyl substituted amides could be obtained directly by quenching a cyclic ester enolate with propylamine.²⁰ This enolate was formed during the enantioselective CA of EtMgBr to coumarins; quenching with propylamine gave the corresponding amide in a good yield without compromising the ee of the enantioselective CA product. Inspired by this result, we envisioned a one pot procedure for the synthesis of β -alkyl substituted amides consisting of first the enantioselective CA of Grignard reagents to an acyclic α,β -unsaturated ester and subsequent *in situ* quenching with an amine to obtain the corresponding amide (Scheme 1). Herein, we present a new one pot method to obtain β -alkyl substituted amides in an asymmetric fashion, in which the

amide formation occurs without the need for additional reagents or reaction steps.

Results and discussion

For this one pot procedure, we focused on the optimisation of the amide formation after the enantioselective CA step, which was carried out with ligand **L1** and $\text{CuBr}\cdot\text{SMe}_2$ at -75°C as previously reported.⁴ We optimised the reaction conditions and determined that the use of 3.0 equiv. of amine and stirring the reaction mixture at room temperature overnight (*ca.* 14 h) were the optimised conditions.

For our investigations, we used α,β -unsaturated esters **1** and **2** as model substrates, because of their high enantioselectivities in the CA of Grignard reagents and as they represent substrates bearing alkyl or aryl substituents.^{21,22}

The enantioselective CA to substrates **1** and **2** was performed, with EtMgBr (1.5 equiv.), $\text{CuBr}\cdot\text{SMe}_2$ (5 mol%) and **L1** (7.5 mol%) in methyl *tert*-butyl ether (MTBE).⁴ Subsequently the intermediate enolate was quenched *in situ* with various amines and allowed to react under the optimised reaction conditions for amide formation (Table 1).

Table 1 Scope for the one pot two step procedure

Entry	Ester	Amine	Product	Yield ^a (%)	ee ^b (%)
1				65	92
2				73	88
3				77 (75) ^c	93 (92) ^c
4				64	87
5				54	93
6				79	91
7				50	93
8				40	98

^a Isolated yields. ^b Determined by chiral GC (entry 1) or chiral HPLC analysis. ^c Carried out on a 7.8 mmol (1.0 g) scale.

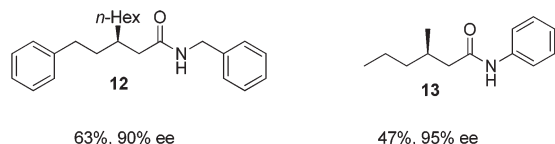


Fig. 2 Different alkyl Grignard reagents.

We found that the reaction of α,β -unsaturated esters **1** and **2** with 3.0 equiv. of aniline provided the corresponding amides **4** and **5** with good yields (65% and 73%, respectively) and excellent enantioselectivities, revealing that no racemisation occurs during the process (entries 1 and 2). The reaction using *p*-bromoaniline furnished amide **6** with good yield (77%) without compromising the ee (entry 3). We also carried out the reaction employing benzylamine and similar results were obtained (entry 4).

In order to broaden the amine scope, the reaction was carried out with the secondary *N*-methylbenzylamine giving rise to the corresponding amides **8** and **9** with synthetically useful yields (entries 5 and 6). Finally, the reaction was performed with aliphatic propylamine, which yields amide **10** in moderate yield and excellent ee (entry 7).²³ In addition, this method has been employed to obtain the biologically active amide **11**²⁴ with 40% yield and 98% ee in a one pot two step synthesis starting from commercially available materials (entry 8).

To underscore the synthetic utility of this method, we performed the one pot synthesis of amide **6** on a large scale (entry 3) starting from 1.0 g (7.8 mmol) of the α,β -unsaturated ester **1** and we obtained 1.8 g (75% yield) of amide **6** with 92% ee.

Finally, we employed different Grignard reagents including the less reactive MeMgBr (Fig. 2). The reaction using *n*-HexMgBr and benzylamine furnished the amide **12** with good yield (63%) and excellent ee. In addition, the Me group is introduced employing the conditions of Loh *et al.*^{5b} followed by the addition of aniline, which afforded the amide **13** in moderate yield (47%) but excellent enantioselectivity.

Conclusions

In conclusion, we have developed a highly enantioselective one pot procedure for the synthesis of β -substituted amides starting from the corresponding α,β -unsaturated esters. This new methodology is based on the previously developed copper-catalysed asymmetric CA of Grignard reagents to α,β -unsaturated esters and the subsequent direct formation of the corresponding amides by quenching the enolate with an amine without the need of extra reagents. This methodology is compatible with a range of α,β -unsaturated esters, Grignard reagents and amines, including primary and secondary amines bearing alkyl or aryl substituents. Importantly, this one pot two-step process occurs without racemisation. Furthermore, the robustness of the process is demonstrated by

performing the reaction on a 1.0 g scale. Further synthetic applications are in progress.

Experimental

General methods

Chromatography: Merck silica gel type 9385 230–400 mesh, TLC: Merck silica gel 60, 0.25 mm. Components were visualized by UV and cerium/molybdenum staining. Mass spectra were recorded on a LTQ Orbitrap XL (ESI+). ¹H- and ¹³C-NMR were recorded on a Varian AMX400 (400 and 100 MHz, respectively) or a Varian Mercury Plus (200 and 50 MHz, respectively) using CDCl₃ as a solvent. Chemical shift values are reported in ppm with the solvent resonance as the internal standard (CHCl₃: δ 7.26 for ¹H, δ 77.16 for ¹³C). Optical rotations were measured using a Schmidt+Haensch polarimeter (Polartronic MH8) with a 10 cm cell (*c* given in g per 100 mL). Enantiomeric excesses were determined by HPLC analysis using a Shimadzu LC-10ADVP HPLC equipped with a Shimadzu SPD-M10AVP diode array detector or by capillary GC analysis (Chiraldex B-PM (30 m \times 0.25 mm \times 0.25 μ m)) using a flame ionization detector. All reactions were carried out under a nitrogen atmosphere using flame-dried glassware and using standard Schlenk techniques. Dichloromethane and MTBE were dried using the solvent purification system SPS 800 from MBraun. Substrates **2** and **3** were synthesised according to literature procedures.^{20,21} Methyl *trans*-cinnamate (**4**), copper salts (CuI and copper(i) bromide dimethylsulfide complex (CuBr)), propylamine and *N*-benzylmethylamine, all Grignard reagents (MeMgBr (3.0 M in Et₂O), EtMgBr (3.0 M in Et₂O), *n*-HexMgBr (2.0 M in Et₂O)), ligands **L2** and **L3** were purchased from Aldrich. The benzylamine was purchased from Acros and aniline from Merck; all amines were distilled before use.

General procedure for the amide synthesis

In a Schlenk tube equipped with a septum and a stirring bar, **L2** (6.7 mg, 10.5 μ mol) and CuBr·SMe₂ (1.85 mg, 9.0 μ mol) were dissolved in MTBE (1.0 mL) and the mixture was stirred under nitrogen at r.t. for 20 min. The mixture was then cooled to –75 °C and the Grignard reagent (0.45 mmol in solution) was added. After stirring for 5 min, a solution of the substrate (0.3 mmol) in MTBE (0.20 mL) was added dropwise over 1 h. After stirring at –75 °C for two additional hours, the corresponding amine (0.9 mmol) was added and the reaction mixture was stirred overnight while being slowly warmed to r.t. Subsequently a saturated aqueous solution of NH₄Cl (2 mL) was added. After extraction with CH₂Cl₂ (3 \times 10 mL) the combined organic phases were dried over MgSO₄ and concentrated under reduced pressure. The crude product was purified using flash chromatography on silica gel (pentane–EtOAc as an eluent) to yield the pure product.²⁵

(*R*)-3-Ethyl-*N*-phenylhexanamide (**4**). Amide **4** was obtained from (*E*)-methyl 2-hexenoate (64 mg, 0.5 mmol) following the general procedure, after purification by column

chromatography on silica (pentane–EtOAc; 9/1), as a pale yellow oil (65%, 71 mg) with 92% ee. $[\alpha]_D^{20} = +47$ (c 1.0 in CHCl_3); ^1H NMR (300 MHz) δ 7.52 (d, $J = 7.9$ Hz, 2H), 7.44–7.18 (m, 2H), 7.08 (t, $J = 7.4$ Hz, 1H), 2.26 (d, $J = 7.0$ Hz, 2H), 2.00–1.82 (m, 1H), 1.50–1.28 (m, 6H), 0.89 (t, $J = 7.3$ Hz, 6H); ^{13}C NMR (50 MHz) δ 171.3 (C=O), 138.0 (C), 128.93 (CH), 124.1 (CH), 119.8 (CH), 42.5 (CH₂), 36.6 (CH), 35.6 (CH₂), 26.2 (CH₂), 19.8 (CH₂), 14.4 (CH₃), 10.8 (CH₃); HRMS (APCI⁺, m/z): calculated for $\text{C}_{14}\text{H}_{22}\text{NO}$ [$\text{M} + \text{H}^+$]: 220.1696, found: 220.1696; enantiomeric excess was determined by chiral HPLC analysis, Chiralcel OD-H column, *n*-heptane–*i*-PrOH 95 : 5, 40 °C, 0.5 mL min^{−1}, 213 nm, retention times (min) t_1 : 34.74 (minor) and t_2 : 38.93 (major).

(R)-3-Ethyl-N-phenyl-5-phenylpentanamide (5). Amide 5 was obtained starting from (*E*)-methyl 5-phenyl-2-pentenoate (95 mg, 0.5 mmol) following the general procedure, after purification by column chromatography on silica (pentane–EtOAc; 9/1), as a pale yellow oil (73%, 102 mg) oil with 88% ee. $[\alpha]_D^{20} = -7$ (c 1.0 in CHCl_3); ^1H NMR (200 MHz) δ 7.50 (m, 3H), 7.21 (m, 7H), 2.78–2.51 (m, 2H), 2.32 (d, $J = 7.0$ Hz, 2H), 2.17–1.83 (m, 1H), 1.83–1.57 (m, 2H), 1.57–1.34 (m, 2H), 0.93 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (50 MHz) δ 171.1 (C=O), 142.5 (C), 138.0 (C), 128.9 (CH), 128.4 (CH), 128.3 (CH), 125.8 (CH), 124.2 (CH), 120.0 (CH), 42.3 (CH₂), 36.6 (CH), 35.2 (CH₂), 33.0 (CH₂), 26.1 (CH₂), 10.7 (CH₃); HRMS (APCI⁺, m/z): calculated for $\text{C}_{16}\text{H}_{26}\text{NO}$ [$\text{M} + \text{H}^+$]: 281.1852, found: 282.1853; enantiomeric excess was determined by chiral HPLC analysis, Chiralcel OD-H column, *n*-heptane–*i*-PrOH 90 : 10, 40 °C, 0.5 mL min^{−1}, 213 nm, retention times (min) t_1 : 12.8 (minor) and t_2 : 14.10 (major).

(R)-N-(4-Bromophenyl)-3-ethylhexanamide (6). Amide 6 was obtained starting from (*E*)-methyl 2-hexenoate (37 mg, 0.3 mmol) following the general procedure, after purification by column chromatography on silica (pentane–Et₂O; 9/1), as a white solid (77%, 69 mg) with 93% ee. $[\alpha]_D^{20} = -9$ (c 1.0 in CHCl_3); ^1H NMR (300 MHz) δ 7.42 (s, 4H), 7.12 (s, NH), 2.25 (d, $J = 7.0$ Hz, 2H), 1.99–1.79 (m, 1H), 1.49–1.12 (m, 6H), 0.94–0.80 (m, 6H); ^{13}C NMR (75 MHz) δ 171.4 (C=O), 136.9 (C), 132.1 (CH), 121.6 (CH), 118.7 (CBr), 42.8 (CH₂), 36.8 (CH), 35.9 (CH₂), 26.5 (CH₂), 20.0 (CH₂), 14.5 (CH₃), 11.0 (CH₃); HRMS (APCI⁺, m/z): calculated for $\text{C}_{14}\text{H}_{21}\text{BrNO}$ [$\text{M} + \text{H}^+$]: 298.0801, found: 298.0803; enantiomeric excess was determined by chiral HPLC analysis, Chiralcel OJ-H column, *n*-heptane–*i*-PrOH 98 : 2, 40 °C, 0.5 mL min^{−1}, 249 nm, retention times (min) t_1 : 47.7 (major) and t_2 : 49.6 (minor).

(R)-N-Benzyl-3-ethyl-5-phenylpentanamide (7). Amide 7 was obtained starting from (*E*)-methyl 5-phenyl-2-pentenoate (58 mg, 0.3 mmol) following the general procedure, after purification by column chromatography on silica (pentane–EtOAc; 9/1), as a pale yellow oil (64%, 42 mg) with 87% ee. $[\alpha]_D^{20} = +8$ (c 1.0 in CHCl_3); ^1H NMR (400 MHz) δ 7.24 (m, 10H), 5.67 (br s, NH), 4.46 (dd, $J = 12.7, 3.8$ Hz, 1H), 4.42 (dd, $J = 12.9, 3.6$ Hz, 1H), 2.62 (td, $J = 13.8, 8.2$ Hz, 1H), 2.60 (td, $J = 13.4, 8.3$ Hz, 1H), 2.21 (dd, $J = 14.3, 7.2$ Hz, 1H), 2.14 (dd, $J = 14.3, 7.2$ Hz, 1H), 1.89 (sept, $J = 6.5$ Hz, 1H), 1.69–1.59 (m, 2H), 1.48–1.33 (m, 2H), 0.91 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (50 MHz) δ 172.3

(C=O), 142.6 (C), 138.4 (C), 128.7 (CH), 128.3 (CH), 128.3 (CH), 127.9 (CH), 127.5 (CH), 125.7 (CH), 43.6 (CH₂N), 41.3 (CH₂), 36.5 (CH), 35.2 (CH₂), 33.0 (CH₂), 26.1 (CH₂), 10.7 (CH₃); HRMS (APCI⁺, m/z): calculated for $\text{C}_{20}\text{H}_{26}\text{NO}$ [$\text{M} + \text{H}^+$]: 296.2009, found: 296.2008; enantiomeric excess was determined by chiral HPLC analysis, Chiralcel OD-H column, *n*-heptane–*i*-PrOH 90 : 10, 40 °C, 0.5 mL min^{−1}, 212 nm, retention times (min) t_1 : 25.12 (minor) and t_2 : 28.53 (major).

(R)-N-Benzyl-3-ethyl-N-methylhexanamide (8). Amide 8 was obtained starting from (*E*)-methyl 2-hexenoate (64 mg, 0.5 mmol) following the general procedure, after purification by column chromatography on silica (pentane–EtOAc; 9/1), as a pale yellow oil (54%, 67 mg) with 93% ee (2 : 3 mixture of conformers A and B). $[\alpha]_D^{20} = +39$ (c 1.0 in CHCl_3); ^1H NMR (400 MHz) δ 7.45–7.20 (m, 4H), 7.16 (d, $J = 7.4$ Hz, 1H), 4.60 (s, NCH_2Ph , conformer A), 4.54 (s, NCH_2Ph , conformer B), 2.94 (s, NCH_3 , conformer B), 2.92 (s, NCH_3 , conformer A), 2.34–2.25 (m, 2H), 2.05–1.78 (m, 1H), 1.45–1.20 (m, 6H), 1.01–0.77 (m, 6H); ^{13}C NMR (50 MHz) δ 173.4 (C=O), 173.0 (C=O), 137.7 (C), 128.9 (CH), 128.5 (CH), 128.0 (CH), 127.5 (CH), 127.2 (CH), 126.3 (CH), 53.4 (CH₂), 50.8 (CH₂), 37.8 (CH₂), 37.5 (CH₂), 36.1 (CH₃), 36.0 (CH₃), 35.8 (CH), 35.7 (CH), 26.3 (CH₂), 26.2 (CH₂), 19.8 (CH₂), 14.4 (CH₃), 10.9 (CH₃); HRMS (APCI⁺, m/z): calculated for $\text{C}_{16}\text{H}_{26}\text{NO}$ [$\text{M} + \text{H}^+$]: 248.2009, found: 248.2015; enantiomeric excess was determined by chiral HPLC analysis, Chiralcel OJ-H column, *n*-heptane–*i*-PrOH 98 : 02, 40 °C, 0.5 mL min^{−1}, 212 nm, retention times (min) t_1 : 13.12 (minor) and t_2 : 13.87 (major).

(R)-N-Benzyl-3-ethyl-N-methyl-5-phenylpentanamide (9). Amide 9 was obtained starting from (*E*)-methyl 5-phenyl-2-pentenoate (95 mg, 0.5 mmol) following the general procedure, after purification by column chromatography on silica (pentane–EtOAc; 9/1), as a pale yellow oil (79%, 122 mg) with 91% ee (4 : 5 mixture of conformers A and B). $[\alpha]_D^{20} = -10$ (c 1.0 in CHCl_3); ^1H NMR (200 MHz) δ 7.31 (m, 10H), 4.60 (s, NCH_2Ph , conformer B), 4.52 (s, NCH_2Ph , conformer A), 2.94 (s, NCH_3 , conformer A), 2.89 (s, NCH_3 , conformer B), 2.61 (m, 2H), 2.35 (m, 2H), 2.16–1.92 (m, 1H), 1.77–1.54 (m, 2H), 1.54–1.35 (m, 2H), 0.94 (t, $J = 5.9$ Hz, 3H, conformer B), 0.87 (t, $J = 5.8$ Hz, 3H, conformer A); ^{13}C NMR (50 MHz) δ 173.3.0 (C=O), 172.7 (C=O), 142.7 (C), 137.6 (C), 136.8 (C), 129.6 (CH), 128.9 (CH), 128.8 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 128.0 (CH), 127.5 (CH), 127.3 (CH), 126.3 (CH), 125.6 (CH), 53.9 (CH₂), 50.9 (CH₂), 37.7 (CH₂), 37.4 (CH₂), 36.0 (CH), 35.4 (CH₃), 35.3 (CH₂), 33.1 (CH₂), 26.3 (CH₂), 26.2 (CH₂), 10.8 (CH₃); HRMS (APCI⁺, m/z): calculated for $\text{C}_{21}\text{H}_{28}\text{NO}$ [$\text{M} + \text{H}^+$]: 310.2165, found: 310.2167; enantiomeric excess was determined by chiral HPLC analysis, Chiralcel OJ-H column, *n*-heptane–*i*-PrOH 95 : 5, 40 °C, 0.5 mL min^{−1}, 212 nm, retention times (min) t_1 : 24.97 (minor) and t_2 : 26.45 (major).

(R)-3-Ethyl-N-propylhexanamide (10). Amide 10 was obtained starting from (*E*)-methyl 2-hexenoate (38 mg, 0.3 mmol) following the general procedure, after purification by column chromatography on silica (pentane–EtOAc; 9/1), as a pale yellow oil (52%, 25 mg) with 96% ee. $[\alpha]_D^{20} = +3$ (c 1.0 in CHCl_3); ^1H NMR (400 MHz) δ 5.49 (s, 1H), 3.22 (t, $J = 6.8$ Hz,

1H), 3.19 (t, $J = 6.6$ Hz, 1H), 2.10–1.98 (m, 2H), 1.82 (m, 1H), 1.57–1.41 (m, 2H), 1.40–1.13 (m, 6H), 0.91 (t, $J = 7.4$ Hz, 3H), 0.88 (t, $J = 6.9$ Hz, 3H), 0.86 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (50 MHz) δ 172.8 (C=O), 41.6 (CH₂), 41.1 (CH₂), 36.5 (CH), 35.6 (CH₂), 26.0 (CH₂), 22.9 (CH₂), 19.7 (CH₂), 14.3 (CH₃), 11.3 (CH₃), 10.7 (CH₃); HRMS (APCI⁺, m/z): calculated for C₁₁H₂₄NO [M + H⁺]: 186.1852, found: 186.1850; enantiomeric excess was determined by chiral GC analysis, Chiraldex B-PM column, T 110 (5 min), 120 (5 min), 130 (5 min), 135 (15 min), ΔT 5 °C min⁻¹, retention times (min) t_1 : 27.54 (major) and t_2 : 28.83 (minor).

(S)-3-Methyl-N-phenethylpentanamide (11). Amide **11** was obtained starting from methyl crotonate (50 mg, 0.5 mmol) following the general procedure, after purification by column chromatography on silica (pentane–Et₂O; 1/1), as a pale yellow oil (40%, 44 mg) with 98% ee. $[\alpha]_{\text{D}}^{20} = +3$ (c 1.0 in CHCl₃); ^1H NMR (400 MHz) δ 7.31 (t, $J = 7.3$ Hz, 2H), 7.24 (d, $J = 7.1$ Hz, 1H), 7.19 (d, $J = 7.3$ Hz, 2H), 5.42 (br s, NH), 3.54 (t, $J = 6.5$ Hz, 1H), 3.53 (t, $J = 6.4$ Hz, 1H), 2.82 (t, $J = 6.8$ Hz, 2H), 2.13 (m, 1H), 2.02–1.78 (m, 2H), 1.42–1.09 (m, 2H), 0.88 (d, $J = 4.7$ Hz, 3H), 0.87 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (50 MHz) δ 172.6 (C=O), 138.9 (C), 128.7 (CH), 128.6 (CH), 126.4 (CH), 44.2 (CH₂), 40.4 (CH₂), 35.8 (CH₂), 32.3 (CH), 29.3 (CH₂), 19.1 (CH₃), 11.3 (CH₃); HRMS (APCI⁺, m/z): calculated for C₁₄H₂₂NO [M + H⁺]: 220.1697, found: 220.1696; enantiomeric excess was determined by chiral HPLC analysis, Chiralcel OD-H column, n -heptane– i -PrOH 98:2, 40 °C, 0.5 mL min⁻¹, 212 nm, retention times (min) t_1 : 28.60 (major) and t_2 : 35.59 (minor).

(R)-N-Benzyl-3-phenethylnonanamide (12). Amide **12** was obtained starting from (*E*)-methyl 5-phenyl-2-pentenoate (58 mg, 0.3 mmol) following the general procedure, after purification by column chromatography on silica (pentane–EtOAc; 9/1), as a pale yellow oil (63%, 67 mg) with 90% ee. $[\alpha]_{\text{D}}^{20} = -1$ (c 1.0 in CHCl₃); ^1H NMR (400 MHz) δ 7.44–7.20 (m, 7H), 7.20–7.03 (m, 3H), 5.64 (br t, $J = 4.8$ Hz, 1H), 4.43 (d, $J = 5.7$ Hz, 2H), 2.62 (t, $J = 6.4$ Hz, 1H), 2.61 (t, $J = 6.3$ Hz, 1H), 2.25–2.12 (m, 2H), 1.97 (m, 1H), 1.72–1.45 (m, 2H), 1.45–1.15 (m, 10H), 0.88 (t, $J = 6.5$ Hz, 3H); ^{13}C NMR (50 MHz) δ 172.4 (C=O), 142.6 (C), 138.4 (C), 128.7 (CH), 128.3 (CH), 128.3 (CH), 127.9 (CH), 127.5 (CH), 125.7 (CH), 43.6 (CH₂), 41.8 (CH₂), 35.7 (CH), 35.3 (CH₂), 33.7 (CH₂), 33.0 (CH₂), 31.9 (CH₂), 29.0 (CH₂), 26.4 (CH₂), 22.7 (CH₂), 14.1 (CH₃); HRMS (APCI⁺, m/z): calculated for C₂₄H₃₄NO [M + H⁺]: 352.2635, found: 352.2632; enantiomeric excess was determined by chiral HPLC analysis, Chiralcel OD-H column, n -heptane– i -PrOH 90:10, 40 °C, 0.5 mL min⁻¹, 212 nm, retention times (min) t_1 : 21.26 (minor) and t_2 : 22.52 (major).

(R)-3-Methyl-N-phenylhexanamide (13). In a Schlenk tube equipped with a septum and a stirring bar, (*S*)-Tol-Binap (10.2 mg, 15 μmol) and CuI (1.91 mg, 10 μmol) were dissolved in MTBE (1 mL) and the mixture stirred under nitrogen atmosphere at r.t. for 20 min. The mixture was then cooled to –20 °C and MeMgBr (2.5 mmol) was added. After stirring for 5 min, a solution of (*E*)-methyl 2-hexenoate (37 mg, 0.3 mmol) in MTBE (0.2 mL) was added dropwise over 1 h. After stirring for two additional hours, the temperature was lowered to –75 °C, the

amine (3.0 mmol) was added and the reaction mixture was stirred overnight while being slowly warmed to r.t. Subsequently a saturated aqueous solution of NH₄Cl (2 mL) was added. After extraction with DCM (3 \times 10 mL) the combined organic phases were dried and concentrated to an oil which was purified using column chromatography on silica (pentane–EtOAc; 9/1), yielding the pure product as a pale yellow oil (47%, 29.2 mg) with 95% ee. $[\alpha]_{\text{D}}^{20} = +1$ (c 1.0 in CHCl₃); ^1H NMR (400 MHz) δ 7.51 (d, $J = 7.9$ Hz, 2H), 7.31 (t, $J = 7.9$ Hz, 2H), 7.08 (t, $J = 7.4$ Hz, 1H), 2.44–2.24 (m, 1H), 2.19–1.97 (m, 2H), 1.45–1.13 (m, 4H), 0.98 (d, $J = 6.3$ Hz, 3H), 0.90 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (50 MHz) δ 171.0 (C=O), 137.9 (C), 128.9 (CH), 124.1 (CH), 119.8 (CH), 45.6 (CH₂), 39.1 (CH), 30.6 (CH₂), 20.1 (CH₂), 19.6 (CH₃), 14.2 (CH₃); HRMS (APCI⁺, m/z): calculated for C₁₃H₂₀NO [M + H⁺]: 206.1539, found: 206.1540; enantiomeric excess was determined by chiral HPLC analysis, Chiralcel OD-H column, n -heptane– i -PrOH 95:5, 40 °C, 0.5 mL min⁻¹, 254 nm, retention times (min) t_1 : 35.38 (minor) and t_2 : 43.70 (major).

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